Kidney International, Vol. 50 (1996), pp. 1694–1699

A randomized controlled study of iron supplementation in patients treated with erythropoietin

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A randomized controlled study of iron supplementation in patients treated with erythropoietin. In view of current uncertainty regarding the optimum route for iron supplementation in patients receiving recombinant human erythropoietin (EPO), a prospective randomized controlled study was designed to investigate this issue. All iron-replete renal failure patients commencing EPO who had a hemoglobin concentration < 8.5 g/dl and an initial serum ferritin level of 100 to 800 μg/liter were randomized into three groups with different iron supplementation: Group 1, i.v. iron dextran 5 ml every 2 weeks; Group 2, oral ferrous sulphate 200 mg tds; Group 3, no iron. All patients were treated with 25 U/kg of EPO thrice weekly subcutaneously. The hemoglobin concentration, reticulocyte count, serum ferritin, transferrin saturation, and EPO dose were monitored every two weeks for the first four months. Thirty-seven patients entered the study (12 i.v., 13 oral, 12 no iron). The three groups were equivalent with regard to age, sex, and other demographic details. Even allowing for dosage adjustments, the hemoglobin response in the group receiving i.v. iron (7.3 ± 0.8 to 11.9 ± 1.2 g/dl) was significantly greater than that for the other two groups (7.2 ± 1.1 to 10.2 ± 1.4 g/dl and 7.3 ± 0.8 to 9.9 ± 1.6 g/dl for Groups 2 and 3, respectively; $P < 0.005$ for both groups vs. Group 1 at 16 weeks). There was no difference between the groups supplemented with oral iron and no iron. Serum ferritin levels remained constant in those receiving i.v. iron (345 ± 273 to 359 ± 140 μg/liter), in contrast to the other two groups in which ferritin levels fell significantly (309 ± 218 to 116 ± 87 μg/liter and 458 ± 206 to 131 ± 121 μg/liter for Groups 2 and 3, respectively; $P < 0.0005$ for Group 1 vs. Group 2, and $P < 0.005$ for Group 1 vs. Group 3 at 16 weeks). Dosage requirements of EPO were less in Group 1 (1202 ± 229 U/kg/16 weeks) than in Group 2 (1294 ± 314 U/kg/16 weeks) or Group 3 (1475 ± 311 U/kg/16 weeks; $P < 0.05$ vs. Group 1). The results of this study suggest that, even in iron-replete patients, those supplemented with i.v. iron have an enhanced hemoglobin response to EPO with better maintenance of iron stores and lower dosage requirements of EPO, compared with those patients receiving oral iron and no iron supplementation.

Anecdotal reports from even the earliest clinical trials of recombinant human erythropoietin (EPO) suggested problems with iron deficiency in patients receiving this treatment. Eschbach and colleagues [1] were the first to draw attention to this problem, with 12 of 25 patients being given intravenous iron dextran as additional iron supplementation. Further studies confirmed this observation [2–5], and it soon became apparent that large amounts of iron were required to support erythropoiesis in patients receiving EPO. Iron supplementation became widely used in such patients, and indeed, most patients starting EPO are now routinely given iron supplements in one form or another [6]. However, the value of this practice has never been assessed by prospective controlled clinical trial.

There has also been much controversy as to whether such iron supplementation is best given orally or intravenously, and in particular whether oral iron supplements can keep pace with the demand. Some authors have found that in the majority of patients oral iron supplementation is adequate [7], while others report a requirement for intravenous iron in a significant proportion of patients treated with EPO [4, 5, 8, 9].

Part of the problem is that there is no reliable marker of functional iron deficiency in patients receiving EPO. The serum ferritin provides a reasonable indicator of iron stores [10], and indeed if this falls below a level of about 30 to 50 μg/liter then absolute iron deficiency is unequivocally present [11]. Functional iron deficiency, however, is now well-recognized in patients receiving EPO, who have adequate iron stores (as judged by a normal serum ferritin level) but who are unable to mobilize iron from these stores rapidly enough to satisfy the demands of the bone marrow [1–3, 6]. The transferrin saturation is theoretically a better indicator of available iron since it reflects the amount of circulating iron in relation to its binding protein in plasma [12]. Previous studies suggested that once the transferrin saturation falls below 16 to 20% then the iron supply for erythropoiesis will be inadequate [13]. However, there is considerable diurnal variation in this biological parameter even in normal subjects [14], so that a value of < 20% may not always indicate iron insufficiency. Other methods of assessing functional iron deficiency have been reported, such as the percentage of hypochromic red cells in the circulation [15, 16], red cell ferritin [17], free erythrocyte protoporphyrin [18], and red cell zinc protoporphyrin levels [19]. Of these, measurement of the percentage of hypochromic red cells is perhaps the most useful since it is an indirect measure of the adequacy of iron supply to the red cell for incorporation into hemoglobin [15, 16]. None of the other tests has proved ideal, and the true incidence of functional iron deficiency in patients receiving EPO is unknown.

It is also possible that, under EPO stimulation, iron supply to the marrow may be a rate-limiting step in the process of erythropoiesis. If so, then administering iron in a readily available form

[1] Deceased

Received for publication June 30, 1995
and in revised form May 31, 1996
Accepted for publication June 3, 1996

(such as intravenous iron dextran) may enhance the hemopoietic response to EPO even in patients who are iron-replete.

To investigate these issues, we set up a prospective randomized controlled study of iron supplementation in iron-replete patients receiving EPO therapy, to compare the effects of using three different regimens of iron treatment: (i) regular intravenous iron supplementation; (ii) regular oral iron supplementation; and (iii) no iron supplementation.

Methods

Patients

Any patient with renal anemia starting EPO therapy was eligible for the study provided they met the following inclusion criteria: (i) Patients on regular hemodialysis (stable for ≥ 3 months), those on CAPD (stable for ≥ 3 months), patients approaching end-stage renal failure but who had not yet commenced renal replacement therapy. (ii) Hemoglobin concentration ≤ 8.5 g/dl on 3 successive occasions. (iii) Normal serum B_{12}; normal serum and red cell folate levels. (iv) Serum ferritin 100 to 800 μg/liter. (v) No other cause for anemia, such as SLE, rheumatoid arthritis, myeloma. (vi) Absence of infection, malignancy, or surgery in last 3 months. (vii) Serum C-reactive protein < 10 mg/liter. (viii) No evidence of severe hyperparathyroidism (that is, plasma PTH < 100 pmol/liter) or aluminium toxicity (plasma aluminium ≤ 0.4 μmol/liter). (ix) Adequate BP control prior to treatment (< 140/90 mm Hg).

Study protocol

The study was approved by the Ethics Committee of St Bartholomew's Hospital.

(i) EPO. All patients were treated with an initial dose of 25 U/kg three times weekly given subcutaneously. In order to minimize the number of dosage adjustments to allow direct comparison of the hemoglobin response among the three groups of patients, this dose was maintained for at least 8 weeks unless the hemoglobin had increased to above 12 g/dl. If this target level was exceeded at any stage of the study, the dose of EPO employed was reduced by one-third; if there had been no significant rise in the hemoglobin concentration (< 1 g/dl) by 8 weeks onwards then the dose of EPO was doubled.

(ii) Iron supplementation. After giving informed consent, patients were randomized to one of three groups: Group 1 patients received an intravenous infusion of iron dextran (Imferon; Fisons Pharmaceuticals, Loughborough, UK) 5 ml, diluted in 100 ml of 0.9% sodium chloride, every two weeks (equivalent to 250 mg of elemental iron). A test dose was given at the start of i.v. iron treatment to check for any possible allergy or anaphylactoid reaction by administering no more than 20 ml of the infusion over the first five minutes. The rate of infusion was then very slowly increased, and the first dose was given over 40 minutes. Subsequent doses were administered over 25 to 30 minutes. Full resuscitation facilities including adrenaline, steroids, and antihistamines were at hand during every infusion of i.v. iron.

Group 2 patients were treated with oral ferrous sulphate 200 mg tds. Compliance was assessed by direct questioning of the patient at each fortnightly visit to the clinic, and by examining the prescribed medication for the number of remaining tablets. Patients were instructed to take their iron tablets with meals to minimize side-effects such as nausea, and were also told to avoid simultaneous administration of phosphate binders.

Group 3 patients were given no iron supplementation.

Table 1. Demographic details of the three groups of patients included in the study

	Intravenous Fe	Oral Fe	No Fe
No. of patients	12	13	12
Sex	6M, 6F	8M, 5F	7M, 5F
Age *years*	47 ± 15	58 ± 16	54 ± 10
Mode of RRT	4 HD	6 HD	5 HD
	7 CAPD	5 CAPD	7 CAPD
	1 pre-dialysis	2 pre-dialysis	
Pre-treatment Hb *g/dl*	7.3 ± 0.8	7.2 ± 1.1	7.3 ± 0.8
Pre-treatment ferritin *μg/liter*	345 ± 273	309 ± 218	458 ± 206
	(119–790)	(140–760)	(120–750)

Assessment

Patients were seen in the outpatient clinic every two weeks throughout the four-month study period. They were questioned regarding their compliance with EPO and oral iron (if relevant), and about the development of any possible side-effects of the treatment. Their blood pressure and weight were checked, and antihypertensive medication was adjusted as required. The current dose of EPO was recorded, and blood was taken for measurement of the following (prior to i.v. iron infusion if relevant): (i) full blood count; (ii) reticulocyte count; (iii) serum ferritin; (iv) serum iron and total iron binding capacity.

End-points

The study was terminated at four months since by then it was anticipated that most patients would have achieved their target hemoglobin concentration. The principal end-points of the study were: (i) hemoglobin response, (ii) iron status, (iii) EPO dosage requirements.

Statistics

Results are expressed as mean ± SD. Analysis of variance and unpaired *t*-tests were used to compare the data at each time point between Groups 1 and 2, Groups 1 and 3, and Groups 2 and 3. A *P* value of less than 0.05 was considered significant.

Results

Patients

Thirty-eight patients were enrolled in the study over a 12 month period. One male hemodialysis patient had a mild anaphylactoid reaction during his first infusion of i.v. iron; this precluded further administration of intravenous iron and he was excluded from further analysis. The remaining 37 patients were randomized as follows: (i) i.v. iron; 12 patients (Group 1); (ii) oral iron; 13 patients (Group 2); (iii) no iron; 12 patients (Group 3).

The three groups were similar with regard to age, sex, and other demographic details (Table 1).

Dosage adjustment of EPO

Despite every attempt to avoid alterations in the dose of EPO, this became necessary in no fewer than 19 of the patients in the study (Table 2). Ten of the patients required an increase in EPO dose due to an inadequate hemoglobin response, 18 of the

Table 2. Number of adjustments in EPO dose required in the 3 groups of patients, with (in brackets) the weeks in which the changes were made

	Intravenous Fe (N = 12)	Oral Fe (N = 13)	No Fe (N = 12)
↑ Dose	1 (8 weeks)	3 (8, 8, 10 weeks)	6 (8, 8, 8, 10, 10, 14 weeks)
No change in dose	6	6	6
↓ Dose	5 (6, 10, 10, 14, 16 weeks)	4 (8, 10, 12, 12 weeks)	0

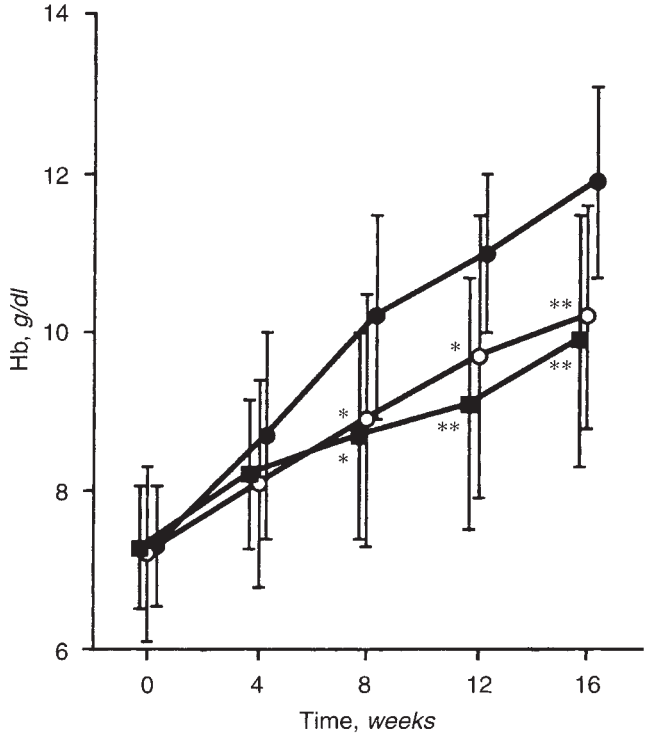

Fig. 1. *Hemoglobin response (mean ± SD) in 3 groups of EPO-treated patients with different regimens of iron supplementation.* Symbols are: (●) i.v. Fe; (○) Oral Fe; (■) No Fe; * $P < 0.05$, ** $P < 0.005$ vs. i.v. Fe treated group.

patients were able to maintain the same dose for the entire duration of the study, and the remaining 9 patients had their dose of EPO reduced when their hemoglobin concentration rose above 12 g/dl. Dosage increases were most frequent in Group 3, less common in Group 2, and rare in Group 1. Reductions in the dose of EPO were slightly more frequent in Group 1 compared with Group 2, and were completely absent in Group 3 (Table 2).

Hemoglobin response

The hemoglobin response in Group 1 was significantly greater than that in the other two groups (Fig 1). This difference became evident at 8 weeks, and persisted throughout the remainder of the study period. There was no significant difference in the hemoglobin response between Groups 2 and 3 at any of the time points throughout the study. There was a slightly enhanced reticulocyte response in Group 1 compared with the other two groups at the start of EPO treatment, but this was not statistically significant (data not shown).

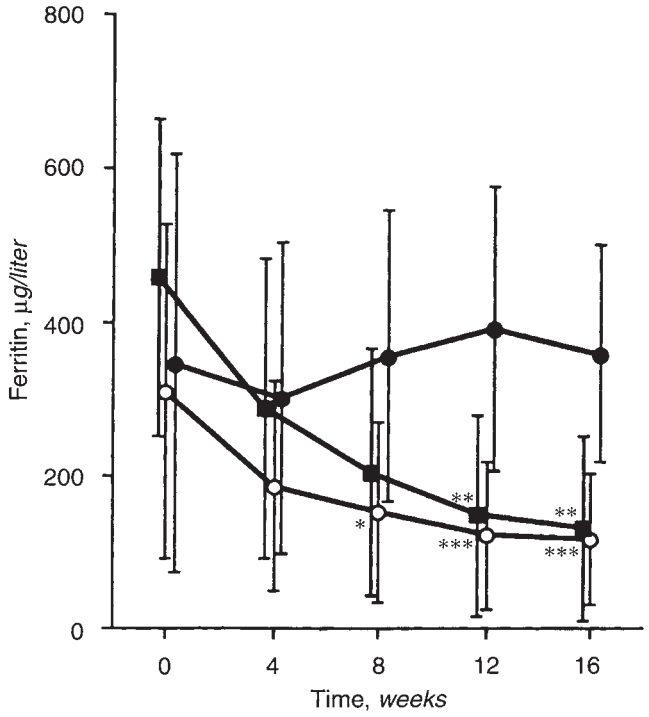

Fig. 2. *Serum ferritin concentrations (mean ± SD) in 3 groups of EPO-treated patients.* Symbols are: (●) i.v. Fe; (■) No Fe; (○) Oral Fe; * $P < 0.05$, ** $P < 0.005$, *** $P < 0.0005$ vs. i.v. Fe treated group.

Serum ferritin levels

The serum ferritin levels remained fairly constant in Group 1, the mean values being maintained at around 300 to 400 µg/liter (Fig 2). In contrast, there was a progressive fall in serum ferritin in the other two groups to a level of around 100 to 200 µg/liter. The mean serum ferritin for Group 2 became significantly lower than that for Group 1 at 8 weeks and this was maintained for the remainder of the study. Similarly, the ferritin levels in Group 3 were significantly less than in Group 1 at 12 and 16 weeks. There were no significant differences in serum ferritin between Groups 2 and 3 at any time points throughout the study.

Transferrin saturation

There was no difference in the mean serum iron, TIBC, or transferrin saturation among the three groups prior to EPO therapy. The transferrin saturation, however, fell in all the groups after EPO was started; this was due to a decrease in serum iron, the TIBC remaining relatively constant (Table 3). The fall in serum iron and transferrin saturation was greater in Groups 1 and 3 than in Group 2, and was evident within four weeks of EPO treatment.

EPO dosage requirements

The mean weekly dose of EPO in Group 1 remained fairly constant at around 75 U/kg throughout the four months of the study (Fig. 3). Slightly, but not significantly, higher doses were

Table 3. Serum iron, TIBC, and transferrin saturation in 3 groups of patients on EPO receiving different regimens of iron supplementation

		Weeks on EPO				
		0	4	8	12	16
Serum iron *μmol/liter*	i.v. Fe	14 (4)	7 (2)	9 (2)	12 (4)	12 (2)
	Oral Fe	13 (2)	13 (2)[b]	12 (2)	11 (3)	15 (4)
	No Fe	13 (4)	8 (3)[c]	7 (3)[c]	8 (3)	9 (3)[c]
Serum TIBC *μmol/liter*	i.v. Fe	55 (8)	52 (6)	50 (4)	48 (7)	52 (4)
	Oral Fe	50 (10)	53 (10)	48 (12)	53 (14)	46 (11)
	No Fe	59 (7)	57 (11)	56 (11)	56 (10)	58 (8)
Transferrin saturation %	i.v. Fe	26 (9)	14 (2)	18 (4)	24 (7)	23 (4)
	Oral Fe	27 (11)	25 (10)[a]	24 (5)	22 (3)	31 (4)
	No Fe	23 (5)	15 (5)	12 (3)[ad]	15 (5)[ac]	15 (6)[d]

Results are expressed as means (SD).
[a] $P < 0.05$ vs i.v. Fe
[b] $P < 0.005$ vs i.v. Fe
[c] $P < 0.05$ vs Oral Fe
[d] $P < 0.005$ vs Oral Fe

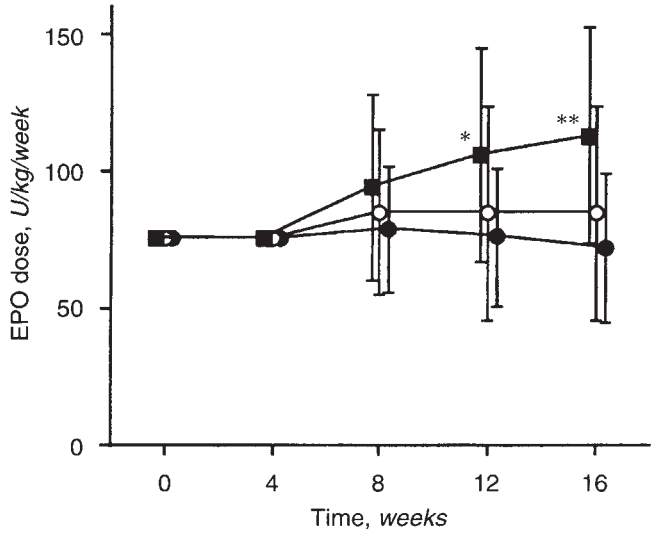

Fig. 3. *Weekly EPO dosage requirements (mean ± SD) in 3 groups of patients.* Symbols are: (■) No Fe; (○) Oral Fe; (●) i.v. Fe; $*P < 0.05$, $**P < 0.01$ vs. i.v. Fe treated group.

used in Group 2, and Group 3 received the highest doses of all. This was statistically significant at 12 and 16 weeks when comparing Groups 1 and 3.

The total amount of EPO used by each patient during the four months of the study is shown in Figure 4. The dosage requirements were less in Group 1 (1202 ± 229 U/kg/16 weeks) than in Group 2 (1294 ± 314 U/kg/16 weeks) or Group 3 (1475 ± 311 U/kg/16 weeks; $P < 0.05$ vs. Group 1 (Fig. 4).

Cost-benefit analysis

For the duration of the study, a total of 1,009,400 units of EPO was used for the patients in Group 1, compared with 1,177,750 units for Group 2, and 1,239,000 units for Group 3. At the prices quoted for EPO and i.v. iron dextran when the study was performed, this represents a total cost of £9,084 for Group 1, £10,599 for Group 2, and £11,151 for Group 3. The average cost of EPO per patient for the 16 weeks of the study was £757 for

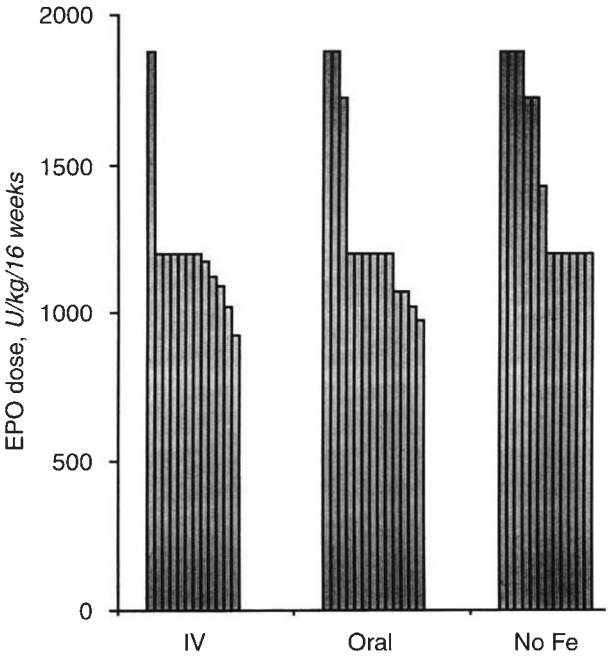

Fig. 4. *Individual total doses of EPO used during the 16-week study period in the 3 groups of patients.*

Group 1, £815 for Group 2, and £929 for Group 3. The total cost of i.v. iron for each patient in Group 1 was £26. Thus, the use of i.v. iron allowed a saving of £32 per patient compared with the use of oral iron, and £146 per patient compared with no iron supplementation. This should be viewed in the light of an enhanced hemoglobin response in Group 1, and since patients in this group had reached their desired hemoglobin in contrast to many of the patients in Groups 2 and 3, further cost-savings would be anticipated following the completion of the study at 16 weeks.

Discussion

This study shows that patients given regular intravenous iron have an enhanced hemopoietic response to EPO compared with those given oral iron supplements or no iron at all. This response was achieved with maintenance of the serum ferritin at relatively constant levels, and the use of marginally lower total amounts of EPO.

Although the results for the group receiving i.v. iron were superior to those given oral iron supplements, one possible weakness of the study may be that compliance might have been incomplete in the group taking oral iron supplements. However, the importance of taking all tablets was emphasized repeatedly to all patients, and monitored closely at each clinic visit. In addition, because of the attention we paid to encouraging compliance, it is likely that we achieved the best compliance possible in a group of patients on EPO. Thus, for practical purposes, even if compliance was not 100%, the level achieved could almost certainly not be bettered in routine clinical practice. Dietary intake of iron was not formally assessed in this study since the amounts ingested would be trivial compared with the amounts contained in the oral and intravenous iron preparations.

The serum iron levels and transferrin saturation were better maintained in the group receiving oral iron compared with that

given i.v. iron. This is probably due to the fact that the latter group received intermittent large boluses of iron which had already been utilized and cleared from plasma during the two weeks prior to blood sampling, in contrast to the continuous mode of administration of the oral iron. It also casts further doubt on the validity of the transferrin saturation measurement, since the "i.v. iron" group achieved the optimum hemoglobin response despite running low transferrin saturations from weeks 4 to 8.

It is interesting to speculate as to why treatment with i.v. iron was so superior to oral iron supplementation. Previous studies have shown that, following infusion, iron dextran is rapidly metabolized, and the iron is released into the reticulo-endothelial system [20]. This iron is then immediately available for erythropoiesis [21]. The bioavailability of oral iron is less clear cut, and in particular iron absorption from the gut may be unreliable. There is currently some controversy over whether oral iron is well-absorbed in renal patients receiving EPO. Earlier studies suggested that iron absorption was enhanced in dialysis patients who were iron-deficient [22, 23]. Skikne and Cook [24] also found that iron absorption was increased by EPO therapy in normal healthy volunteers, although two studies have suggested impaired absorption in dialysis patients on EPO [25, 26]. Thus, although iron absorption would appear to be enhanced in *absolute* iron deficiency, the situation is less clear in patients who are *functionally* iron-deficient (that is, normal iron stores, but an inability to release iron rapidly enough to satisfy the demands of the marrow). All the patients in this study were iron-replete with an initial serum ferritin > 100 μg/liter, and thus it is possible that iron absorption in this cohort of patients was impaired.

The fact that it was possible to enhance erythropoiesis with intravenous iron supplementation in this group of iron-replete patients suggests that iron supply to the marrow is a rate-limiting step in the process of erythropoiesis. It seems apparent that regular oral iron supplementation is unable to produce this effect, almost certainly due to differences in bioavailability between orally- and intravenously-administered iron. The lack of any significant benefits of oral iron compared with no iron supplementation was surprising, and suggests that there is no great advantage in patients with initial serum ferritin levels > 100 μg/liter taking oral iron supplements, other than a possible slight saving in EPO dosage requirements. However, it is possible that once the serum ferritin level falls with EPO treatment, the bioavailability of oral iron may increase, and there may then be a role for oral iron supplements.

The regimen for administering intravenous iron in this study was arbitrary, and there is no evidence that fortnightly infusions of 5 ml iron dextran represent the optimum method. We selected this regimen since it was practical (the patients were attending for review on a fortnightly basis, and it was convenient to give one vial of 5 ml iron dextran at each visit). The fact that the mean serum ferritin levels did not change appreciably during the study suggests that all the intravenous iron given was being consumed in the process of erythropoiesis, since any excess of iron would have been reflected in a rise in serum ferritin. It would clearly have been possible to give the entire 40 ml of iron dextran (analogous to a total dose iron infusion) at the start of EPO therapy although there is no guarantee that it would have had the same effect. There are theoretical reasons, however, why the more frequent, lower-dose regimen might be preferable. Administering a large single bolus of parenteral iron would result in all but a small fraction ending up in reticulo-endothelial stores. There may theoretically be difficulties in releasing the iron from these stores again when it is needed, since many factors such as infection and inflammatory disease can interfere with this process [27]. Large boluses of intravenous iron also commonly cause arthralgia and other side-effects [28]. Giving frequent but smaller boluses ensures a slow but steady supply of readily available iron to the marrow.

The results from this study suggest that it may be cost-effective to use intravenous iron supplementation more widely in patients commencing EPO, considering the relative costs of EPO and iron dextran. The present evidence suggests that this is valid even in the absence of any laboratory evidence of iron insufficiency. However, this has to be weighed against the disadvantages of adopting a "regular i.v. iron" protocol, namely the time and labor involved in setting up and supervising the iron infusions, the inconvenience to the patient of regular visits to the hospital, and the small but significant risk of serious adverse effects such as anaphylactic reactions. Furthermore, this study sought to investigate the potential benefits of intravenous iron supplementation in the correction phase of EPO therapy only; it would be inappropriate to extrapolate these conclusions to the maintenance phase of treatment, which would require a separate study.

In any patient who is responding poorly to EPO in the absence of any identifiable cause, however, it would seem reasonable to consider a trial of intravenous iron supplementation, with close monitoring of the subsequent response. Although there is some concern regarding allergy and anaphylactic reactions to iron dextran, other parenteral iron compounds are becoming more widely available [29], which are likely to share the same benefits in terms of enhancing the response to EPO.

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